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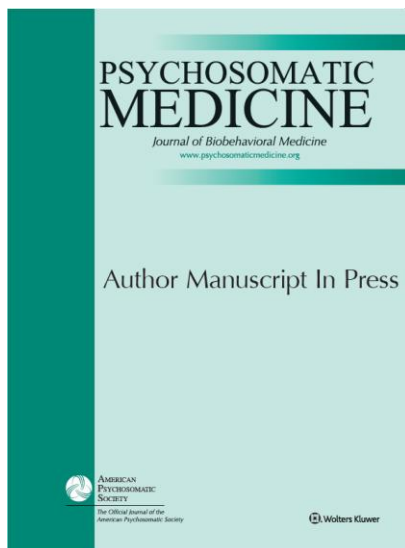
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Brain-Heart Pathways to Blood Pressure-Related Hypoalgesia

Cristina Ottaviani, Ph.D.^{1,2}, Sabrina Fagioli, Ph.D.¹, Eugenio Mattei, Ph.D.³, Federica Censi Ph.D.³,
Louisa Edwards, Ph.D.⁴, Emiliano Macaluso, Ph.D.^{1,5}, Marco Bozzali, M.D.¹, Hugo Critchley, D.Phil.⁶,
Giovanni Calcagnini Ph.D.³

¹ *Neuroimaging Laboratory, IRCCS Santa Lucia Foundation, Rome, Italy*

² *Department of Psychology, Sapienza University of Rome, Rome, Italy*

³ *Department of Cardiovascular, Dysmetabolic and Aging-associated Diseases, Italian Institute of Health, Rome, Italy*

⁴ *Institute of Metabolism and Systems Research, College of Medical and Dental Sciences, Birmingham University, Birmingham, UK*

⁵ *ImpAct Team, Lyon Neuroscience Research Center, Lyon, France*

⁶ *Department of Neuroscience, Brighton and Sussex Medical School, University of Sussex, Brighton, UK*

Address correspondence and reprint requests to Cristina Ottaviani, Department of Psychology, via dei Marsi 78, 00185 Rome, Italy. E-mail: cristina.ottaviani@uniroma1.it. Tel: +39 3474454366; Fax: +39 06 4991 7711.

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Abstract

Objective: High blood pressure (BP) is associated with reduced pain sensitivity, known as BP-related hypoalgesia. The underlying neural mechanisms remain uncertain, yet arterial baroreceptor signaling, occurring at cardiac systole, is implicated. We examined normotensives using functional neuroimaging (fMRI) and pain stimulation during distinct phases of the cardiac cycle to test the hypothesized neural mediation of baroreceptor-induced attenuation of pain.

Methods: Eighteen participants (10 women; 32.7 ± 6.5 years) underwent BP monitoring over one week at home, and individual pain thresholds were determined in the lab. Subsequently, participants were administered unpredictable painful and non-painful electrocutaneous shocks (stimulus type), timed to occur either at systole or diastole (cardiac phase) in an event-related design. After each trial, participants evaluated their subjective experience.

Results: Subjective pain was lower for painful stimuli administered at systole compared to diastole, $F_{1, 2283} = 4.82$; $p = 0.03$. Individuals with higher baseline BP demonstrated overall lower pain perception, $F_{1, 2164} = 10.47$; $p < 0.0001$. Within the brain, painful stimulation activated somatosensory areas, prefrontal cortex, cingulate cortex, posterior insula, amygdala, and the thalamus. Stimuli delivered during systole (concurrent with baroreceptor discharge) activated areas associated with heightened parasympathetic drive. No stimulus type x cardiac phase interaction emerged except for a small cluster located in the right parietal cortex.

Conclusions: We confirm the negative associations between BP and pain, highlighting the antinociceptive impact of baroreceptor discharge. Neural substrates associated with baroreceptor/BP-related hypoalgesia include superior parietal lobule, precentral and lingual gyrus, regions typically involved in the cognitive aspects of pain experience.

Key words: Blood Pressure, Hypoalgesia, Pain, Baroreceptors; fMRI.

Acronyms: **BP** = blood pressure; **BMI** = body mass index; **fMRI** = functional magnetic resonance imaging; **STAI** = Spielberger Trait Anxiety Inventory; **CES-D** = Center for Epidemiologic Studies Depression Scale; **PCS** = Pain Catastrophizing Scale; **BPI** = Brief Pain Inventory; **ECG** = electrocardiogram; **VAS** = Visual Analog Scale; **BOLD** = Blood-Oxygen-Level Dependent; **SD** = Standard Deviation; **SBP** = Systolic Blood Pressure; **ANOVA** = Analysis of Variance; **CAN** = Central Autonomic Network.

INTRODUCTION

Blood pressure (BP) elevation is associated with decreased pain, termed BP-related hypoalgesia. This phenomenon is observed in preclinical studies of rodents (1), in unmedicated hypertensive patients (2), and people with family history of hypertension (3). BP-related hypoalgesia is elicited by spontaneous (4) or experimentally-induced BP increases (5) in normotensive individuals, and is reported in infants and adolescents (6,7).

However, debate remains regarding the concept of BP-related hypoalgesia, and its reliability (2,8). Not all animal or human studies reproduce BP-related hypoalgesia (9-11). To complicate matters, the relationship between hypertension and pain sensitivity appears reversed in patients with chronic pain disorders (12).

Importantly, pain is a critical signal of acute cardiovascular pathology (e.g. angina). BP-related hypoalgesia may make 'at-risk' hypertensive individuals less aware of vital symptoms. Indeed, reduced pain interferes with early detection of silent (asymptomatic) myocardial ischemia and infarction; conditions are nearly twice as common in hypertensives (13). Moreover, in coronary artery disease, BP at rest and during physical activity shows an inverse relationship with chest pain (14,15). Longitudinal studies suggest a pathophysiological link between hypertension and hypoalgesia (16), indicating that elevated BP may be caused by, rather than be a consequence of, reduced pain (8). Plausibly, hypertension develops through instrumental learning, reinforced by the associated reduction in pain (1).

The neural mechanisms underlying BP-related hypoalgesia are unclear. Arterial baroreceptors are implicated. These mechanoreceptors, in the aortic arch and carotid sinus, drive the afferent component of the baroreflex regulation of BP (17). First, artificial stimulation of carotid baroreceptors results in

reduced pain perception in hypertensives and normotensives (18). Second, natural stimulation of baroreceptors by increases in BP during cardiac systole is associated with dampened pain and nociception (19-21). Third, pharmacological denervation of baroreceptors blocks the BP-pain association (1). Lastly, the same set of brain regions (periaqueductal gray, amygdala, insula) are implicated in both baroreceptor control and pain processing (22,23). These observations do not however prove causality.

Hypertension is a leading cause of death worldwide motivating the need to define the mechanisms linking BP to pain. Focusing on the putative role of baroreceptor signaling, we examined normotensive individuals, obtaining subjective and neural correlates of pain. Pain stimulation was delivered to coincide with the presence or absence of natural phasic baroreceptor activation; i.e. at ventricular systole during the ejection of blood from the heart, or at diastole when spontaneous baroreceptor activity is minimal. We tested the hypothesis that systolic baroreceptor signals attenuate subjective and neural correlates of pain. Moreover, we predicted that this effect is amplified in individuals with higher BP and that, at a neural level, the activity of brainstem autonomic nuclei, amygdala, and anterior insula mediates this BP-related hypoalgesia (23).

METHODS AND MATERIALS

Participants

Hospital employees and students were invited to participate in a study of “*the physiological correlates of pain*”. Of 22 participants who agreed to take part, four did not meet inclusion criteria ($n = 2$) or were excluded from the analyses due to technical problems ($n = 2$). The final sample consisted of 18 right-handed normotensive participants (10 women; mean age 32.7 ± 6.5 years; range: 24-42 years). All subjects were White. Exclusionary criteria, assessed during a pre-screening questionnaire, were:

doctor diagnosis of hypertension; history of cardiovascular disease, diabetes, liver or kidney disorders, or opiate dependence; diagnosis of psychiatric disorders (current and/or past); use of anti-hypertensive medications or narcotics, use of drugs/medications that might affect cardiovascular function; obesity (body mass index $> 30 \text{ kg/m}^2$); menopause; use of oral contraceptives during the previous 6 months, and pregnancy or childbirth within the last 12 months. Participants were compensated (€30) for their time. The research protocol was approved by the Bioethical Committee of Santa Lucia Foundation (CE/PROG 523).

Procedure

Data collection occurred between November 2016 and February 2017. After eligibility assessment, the fMRI session appointment was scheduled. Participants were asked to refrain from alcohol and use of analgesic or anti-inflammatory medications for 24 hours prior to the study; and from caffeine, alcohol, and vigorous exercise for two hours before the experiment. To avoid circadian influences, all sessions were scheduled in the afternoon. Participants came to the lab, read and signed the informed consent form, and completed socio-demographic and psychometric questionnaires. They then entered the MRI scanner room, were instrumented for physiological recording, and underwent pain threshold assessment, following which the imaging protocol started. At the end of the session, participants were instructed how to perform daily self-measurement of BP. After one week of home BP assessment, they returned the BP device to the laboratory, were debriefed, and received monetary compensation.

Psychometric Questionnaires

A set of standardized questionnaires were administered to investigate whether pain ratings were associated with specific psychological traits: a) Spielberger Trait Anxiety Inventory (STAI) (24) as a measure of dispositional anxiety (Cronbach's $\alpha = 0.87$); b) Center for Epidemiologic Studies

Depression Scale (CES-D) (25) as a measure of depressive symptoms ($\alpha = 0.85$); c) Pain Catastrophizing Scale (PCS) (26) as a measure of exaggerated and ruminating negative cognitions and emotions during pain (Total score: $\alpha = 0.88$; Helplessness subscale: $\alpha = 0.84$; Rumination subscale: 0.75; Magnification subscale $\alpha = 0.63$); and d) Brief Pain Inventory (BPI) (27) as a measure of participants' pain on the day of the experimental session ($\alpha = 0.69$).

Home BP assessment

Following NICE guidelines for home BP assessment (28), participants recorded two morning and two evening BP readings for one week using an electronic self-measurement device that transmitted measurement data to a remote server via 3G/GPRS connection for storage and analysis (MyPress; Cardionica, Italy).

Physiological signal acquisition

Electrocardiogram (ECG), pulseoximetry, respiration, and electrical stimulation current pulses were recorded simultaneously with fMRI (Biopac Systems Ins, USA) and stored on a PC using a NI-cRIO 9911 system (National Instrument, USA).

Real time ECG R-wave detection and stimuli synchronization were implemented using custom software (LabVIEW 2011, National Instruments, USA) on the cRIO. QRS detection from the ECG used a derivative + threshold algorithm from lead II.

Pain threshold determination and electrocutaneous stimulation

Pulses of electrocutaneous stimulation were delivered to the left lateral antebrachial cutaneous nerve with two Ag-AgCl electrodes using the Biopac System. To determine pain threshold, participants

rated the intensity of sequential stimulation on a 10-point intensity rating scale (0 = don't feel anything, 9 = very painful). Pulse duration was 5 ms and the intensity was increased at a constant rate until a rating of 9 (very painful) was obtained. The process was then repeated with decreasing steps at the same rate (2 increasing and 2 decreasing ramps).

During the fMRI session, each pulse had a fixed duration of 5 ms and variable amplitude according to the participant's pain threshold (i.e. 80% and 200% of average pain threshold for non-painful and painful stimuli, respectively). The actual current delivered for each pulse was measured using a current probe (80i-110s AC/DC Current Probe, Fluke, USA). Pulses were delivered either at late diastole (on the R-wave) or at ventricular systole (300 ms after the R-wave). R-wave detection and pulse synchronization were displayed online on a PC screen for visual checking. The average current provided was 22.2 mA and the maximum stimulation intensity was 40 mA.

Experimental task and fMRI paradigm

Participants lay within the scanner bore in low light. They were instructed to focus on a central fixation point and wait for the upcoming sensory stimulus (electrocutaneous pulse). All visual stimuli were projected onto a translucent screen at the back of the MR bore and were visible through a mirror mounted on the head coil. At the beginning of each block, a white central fixation point was displayed on a black background for 6, 8, 10 or 12 s and was followed by a 5 ms electric pulse. Each of these time lags was used for each experimental condition and pseudo-randomized across trials. There was a 2 s interval between the stimulus delivery and the start of the VAS rating. The VAS consisted of a green horizontal bar (visual angle = 12°) displayed for 3 s at the center of the screen. Nine equidistant white ticks were depicted below the horizontal bar associated with nine white digits. The digits 1 to 9 were depicted from the left to the right and were used to rate increases in pain intensity from "Not painful at all" to "Very painful". These two descriptors were displayed at the left and right side of the bar. When

the rating scale appeared on screen, a small white asterisk was displayed at the center of the bar, corresponding to a score of 5. Participants rated the peak pain intensity by pressing the right button with their right middle finger to move the asterisk towards the right side of the bar (higher pain scores), and the left button with their right index finger to move it toward the left side of the bar (lower pain scores).

All participants underwent two fMRI scanning runs (lasting approximately 15 min). Each fMRI run comprised 64 trials consisting of 32 unpredictable pain and 32 non-pain stimuli, timed to occur either at systole ($n = 16$ pain, $n = 16$ non-pain) or diastole ($n = 16$, $n = 16$ non-pain).

Image acquisition and preprocessing

Functional neuroimaging datasets were acquired with using a 3T Allegra scanner (Siemens, Erlangen, Germany). Blood oxygenation level dependent (BOLD) contrast was obtained using echo-planar T2*-weighted imaging (EPI). The acquisition of 32 transverse slices (2.5 mm thick, 50% distance factor), with a repetition time of 2.08 sec, provided coverage of whole brain. The in-plane resolution was 3 x 3 mm.

The fMRI datasets were processed with SPM12 (www.fil.ion.ucl.ac.uk). The first four image volumes of each run were discarded to allow for stabilization of longitudinal magnetization. The remaining 858 volumes were realigned with the first volume and the acquisition timing was corrected using the middle slice as reference. To allow inter-subject analysis, all images were normalized to the Montreal Neurological Institute (MNI) standard space (29), using the mean of all 858 images. All images were smoothed using an isotropic Gaussian kernel (full width at half maximum = 8 mm). Caution taken to avoid the impact of head movements and any shift between the onset of all the

relevant events, and reasons to exclude biases due to pulsatile movements in the brain are detailed in the supplementary material (Text, S1 and S2, in Supplemental Digital Content, <http://links.lww.com/PSYMED/A463>).

Behavioral data

Behavioral data are expressed as means \pm SD. Differences at $p < 0.05$ were regarded as significant.

Analyses were performed with the software modules of SPSS 23 (IBM) and SAS Institute. First, sex differences were analyzed by t and χ^2 tests. Second, Pearson correlations were run to test for associations between dispositional characteristics and the main study variables (average weekly SBP, pain threshold, and subjective pain evaluation by the VAS).

Random effects regression models (PROC MIXED; SAS Institute) examined the relation between repeated pain evaluations (VAS), Stimulus type (pain vs no pain), and Cardiac phase (systole vs diastole). To test if cardiac cycle-related pain modulation was moderated by BP, the model was repeated including average weekly BP for each participant as a predictor.

fMRI data analysis

Statistical inference used random effects approach (30). This comprised two steps. First, for each participant, data were best-fitted (least-square fit) at every voxel using a linear combination of effects of interest. These encompassed the timing of sensory stimuli for each of the four event-types (given by crossing of the two factors): 1) pain at systole (S/P); 2) no-pain at systole (S/nP); 3) pain at diastole (D/P); 4) no-pain at diastole (D/nP). Additionally, to assess the impact of the subjective pain ratings, the model included one regressor that modelled the onset of the VAS rating for each trial (event

duration = 0) and its parametric modulator, as indexed by the numerical VAS rating of the peak pain intensity at each trial. The analytic model also included head-motion realignment parameters as covariates of no interest. All event-types were convolved with the SPM12 standard hemodynamic response function (HRF). Linear compounds (contrasts) determined the effect of the four relevant trial-types and the parametric regressor, averaged across the two fMRI runs.

Repeated-measures ANOVA was used to analyze the event-related activations associated with the main four event-types. The VAS and the corresponding parametric modulation were assessed using two separate one-sample *t*-tests (Text S3, Table S1, Table S2, in Supplemental Digital Content, <http://links.lww.com/PSYMED/A463>). Correction for non-sphericity was used to account for possible differences in error variance across conditions and any non-independent error term from repeated measures (31).

Within the group-level ANOVA, we first assessed the overall main effect of pain by contrasting all pain-delivery conditions against the no-pain conditions, irrespective of cardiac phase ($[(S/P + D/P) > (S/nP + D/nP)]$ and the inverse: $[(S/nP + D/nP) > (S/P + D/P)]$). Moreover, we assessed the overall main effect of baroreceptor discharge, contrasting all conditions in which stimulation was delivered at systole against conditions where the stimulus was delivered at diastole, irrespective of stimulus type ($[(S/P + S/nP) > (D/P + D/nP)]$ and the inverse: $[(D/P + D/nP) > (S/P + S/nP)]$). Second, we asked whether pain-related brain activity was modulated by baroreceptor discharge. We tested the interaction between these two factors, expecting maximal brain activity within pain-related areas at diastole, when the spontaneous discharge of baroreceptor was minimal; $[(D/P - D/nP) > (S/P - S/nP)]$. To verify whether cardiac cycle-related pain modulation was moderated by average weekly BP, we performed a

group-level one-sample t-test (i.e., considering the contrast images for the interaction term $[(D/P - D/nP) > (S/P - S/nP)]$ and entered mean BP value of each participant as covariate in the model.

For these comparisons, the SPM threshold was set to p -corrected < 0.05 (Family Wise Error at the voxel-level) for the whole brain.

ROI-based analysis

To further interpret our results, we performed targeted region of interest (ROI) analyses. Specifically, we tested all pain-modulation effects in nine ROIs belonging to the “pain matrix”, including insula, anterior cingulate cortex (ACC), primary and secondary somatosensory areas, cerebellum, parietal operculum, premotor and supplementary motor cortices, amygdala and thalamus (32,33). ROIs were created using SPM Anatomy Toolbox version 2.2c (34). Corrected p -values for each ROI were assigned using a Small Volume Correction procedure, considering each ROI as volume of interest (35).). P -values were Bonferroni-corrected for multiple comparisons ($0.05/9$).

Moreover, given our prior hypothesis concerning the possible involvement of descending inhibitory control (i.e., PAG/RVM) on pain modulation, we used a small volume correction procedure to test for the effect of pain and cardiac cycle-related pain modulation specifically for this pathway. The search volume for this area was derived from previous work (36) centering a sphere at MNI $x, y, z = 18 -30 -30$; with a radius of 10 mm.

RESULTS

Descriptive statistics

Participants had a mean SBP of 112.03 ± 5.95 mmHg, mean diastolic BP of 71.16 ± 6 mmHg, and

a mean heart rate of 70.21 ± 6.4 bpm. The average pain threshold was 22.49 ± 7.15 mA. Women had lower BMI (21.7 ± 3.8 Kg/m²) compared to men (25 ± 2.7 Kg/m²), $t(16) = 2.1$; $p = .05$. No other sex differences emerged; therefore, this variable was not included as a covariate in the random-effects regression models.

Pain catastrophizing was negatively associated with SBP ($r = -0.84$) and positively associated with subjective pain perception during painful stimulation ($r = 0.47$). An inverse association emerged between the helplessness subscale and SBP ($r = -0.91$). SBP was negatively correlated with pain ratings ($r = -0.80$) and marginally associated with pain threshold ($r = 0.79$). Table 1 shows Pearson correlations between dispositional characteristics and average weekly SBP, pain threshold, and subjective pain rating.

Behavioral ratings

There was a main effect of Stimulus type ($F(1, 2283) = 3684.7$; $p < 0.0001$), and a Stimulus type by Cardiac phase interaction, ($F(1, 2283) = 4.82$; $p = 0.03$). Non-painful stimuli were naturally perceived as less painful (2.8 ± 1.9) compared to painful stimuli (6.8 ± 1.7). Moreover, painful stimuli were perceived as less painful during baroreceptor discharge, i.e. at systole (6.1 ± 1.7), compared to diastole (6.9 ± 1.7).

When individual difference in SBP was incorporated into the statistical model, a main effect of SBP was revealed, $F(1, 2164) = 166.76$; $p < 0.0001$, and a Stimulus type by SBP interaction, $F(1, 2164) = 10.47$; $p < 0.0001$. Participants with higher SBP manifested lower pain perception compared to those with lower SBP and this was particularly true for painful stimuli. Neither Cardiac phase by SBP group, nor Cardiac phase by Stimulus type by SBP group (3-way) interactions emerged.

FMRI

Overall pain-related activation

Pain stimulation enhanced activity of cortical and subcortical regions (Table 2; Figure 1A). In the frontal lobe, one activation cluster extended from the lateral surface of the hemisphere to the depth of the central sulcus, and extended to the opposite hemisphere embracing, anteriorly, the precentral gyrus and, posteriorly, somatosensory areas within superior parietal lobe (Text, S1 and S2, Supplemental Digital Content, <http://links.lww.com/PSYMED/A463>). Pain stimulation also enhanced activity within midcingulate cortex and prefrontal cortex, including supplementary motor cortex bilaterally. Another activation cluster was located in the cerebellum and extended superiorly to occipital cortex. Pain stimulation also enhanced activity within the thalamus, left amygdala, hippocampus, bilateral posterior insula and the right posterior cortex, including the supramarginal gyrus (SMG). No regions showed significantly greater activity to the non-pain vs pain stimuli.

The ROI approach revealed signal increase in the posterior insula (bilaterally), the somatosensory cortices, the premotor and supplementary cortices, the parietal operculum, the cerebellum and the thalamus. Signal increases in amygdala and middle cingulate cortex were also significant but did not survive Bonferroni correction (Table 3). Results also revealed signal increase in the PAG/RVM (maxima $x,y,z = 20 -36 -24$; $Z\text{-value} = 4.53$; $p < 0.001$, corrected for small volume), consistent with the putative pathway for descending inhibitory control of pain.

Overall effect of baroreceptor discharge

Irrespective of stimulus type, we found that, within the left parietal lobe, the postcentral gyrus, possibly encompassing secondary somatosensory cortex ($x,y,z = -58 -10 18$; $z\text{-value} = 4.27$; Cluster size: 236; $p\text{-corr} = 0.016$) and a cluster located in the superior parietal lobe, possibly including the

primary sensory cortex (i.e., BA2) ($x,y,z = -16 -50 54$; $z\text{-value} = 4.17$; Cluster size: 186; $p\text{-corr} = 0.039$) activated at ventricular systole, during spontaneous baroreceptor discharge (Figure 1B). This analysis did not highlight any activity within the ROI chosen to test any involvement of the descending inhibitory pathways. Furthermore, the comparison contrast for the effect of minimal over maximal baroreceptor discharge (i.e. diastole vs systole) was not significant.

Cardiac cycle-related pain modulation

Next, we tested whether neural responses to pain were selectively modulated by the cardiac phase. Analysis revealed no significant activation associated with modulation of pain by baroreceptor discharge, nor ROI-based approach highlighted engagement of regions that are known to be involved in pain perception, including PAG/RVM descending inhibitory pathway. Analysis exploring the impact of SBP variability on pain modulation did not reveal significant brain activation, suggesting that the cardiac cycle-related pain modulation is not affected by subtle changes in BP among our sample of healthy participants. Although the interaction between Stimulus type and Cardiac phase did not reveal a significant effect, due to its theoretical significance, we report the activation of a small cluster located in the right parietal cortex, likely to include the posterior division of the supramarginal gyrus (SMG: $x,y,z = 34 -40 20$; $z\text{-value} = 4.10$; Cluster size: 127; $p\text{-unc} < .001$). Specifically, we found that the activity within this area increased for pain stimuli delivered at diastole, and decreased significantly for non-pain stimuli delivered at diastole. This result suggests that the activity within this region was increased when pain stimuli were presented at diastole compared to other conditions.

DISCUSSION

The present study supports the existence of a relationship between baroreceptor activation, BP and pain perception, in a predicted direction, i.e. pain perception is lower in the presence of elevated BP.

Our data shows that the inverse relationship between BP and pain perception is not exclusive to hypertensive individuals but is also present in normotensives (4). First, we observed an inverse correlation between basal (weekly home) SBP and lower subjective pain ratings (determining pain threshold) during electrical stimulation. Next, in line with the idea that BP-related hypoalgesia is coupled to the baroreflex, painful stimuli were generally perceived as less painful during baroreceptor discharge (i.e. ventricular systole).

In normotensives, an association is observed between natural variations in baroreceptor activity across the cardiac cycle and objective nociceptive responding (19,37-39). However, subjective pain ratings may not show such variation across the cardiac cycle (19,38,39) or even occur in the opposite direction (i.e. higher pain ratings at systole compared to diastole) (40). To our knowledge, this is the second study to report reduced subjective pain perception during natural baroreceptor discharge (21). Our data show a main effect of cardiac phase, but not a stimulus type by phase interaction. This may suggest that the influence of natural baroreceptor activation on stimulus perception extends beyond pain (41). However, non-painful stimuli in our study were not rated as completely free of pain. Moreover, the stimuli we used here had an average higher voltage compared to previous studies on this topic. This methodological discrepancy may partly explain divergence of results. Further, our result is consistent with data on reduced pain after artificial stimulation of baroreceptors (42-44). However, even this finding is variable with some studies reporting opposite effects of baroreceptors stimulation on pain perception (38,45,46). When BP was taken into account in the current study, pain perception, especially for painful stimuli, was dampened in participants with higher SBP. However, this did not differ based on cardiac cycle phase. Indeed, if elevated BP is caused by reduced pain perception, it is plausible that such progression to disease due to reduced pain sensitivity does not occur as early as in

present participants' age or perhaps occur in those already diagnosed as hypertensive (i.e., in earlier onset hypertension) and therefore excluded from the study.

Another recent plausible explanation that needs to be further investigated is that hypoalgesia in hypertension-prone individuals is explained by altered stress response rather than by differential baroreflex activation (47).

Pain perception has specific signatures in terms of brain network activation. Thus, functional imaging reveals how the experience of pain is different with varying baroreceptor discharge. Irrespective of cardiac timing, the painful stimuli activated regions involved in processing pain, including somatosensory areas, prefrontal cortex, cingulate cortex, posterior insula, amygdala and thalamus, the primary relay for afferent transmission of nociceptive information (48). Importantly, in agreement with existing literature claiming a role for descending inhibitory pathway in pain perception, results revealed a significant signal increase in the PAG/RVM (49). Relevant to the aim of the present study, most of these structures form the core of the Central Autonomic Network (CAN) (50). Moreover, present data support recent perspectives including cerebellar involvement in pain perception (51). Again, cerebellum is also implicated in autonomic regulation (52).

Irrespective of stimulus type (painful or non-painful) baroreceptor discharge was mainly associated with activation of the left superior parietal lobule and postcentral gyrus, areas that have been associated with increased high-frequency power (parasympathetic) heart rate variability (53,54).

Previous studies that looked at the brain correlates of BP-related hypoalgesia mostly examined the effects of baroreceptor stimulation by neck suction on pain-related evoked brain potentials. Results

point to the fact that stimulation of the arterial baroreceptors can modulate processing of noxious stimuli but results were in the opposite direction (55). Only one study examined variations in the N2-P2 amplitudes across the cardiac cycle and reported smaller amplitudes mid-cycle, indicating that cortical processing of nociception was attenuated during systole compared to diastole (20). Gray and colleagues, however, found that P2 was abolished for stimuli presented during baroreceptor activation, but only when nociceptive stimuli were preceded by a warning cue cued, and therefore expected (56). The latter is the only study in which attentional and baroreceptor influences on pain were dissected and the authors conclude that the “analgesic” effects of baroreceptor activation obligatorily require salient or attentionally-focused pain (56). For completeness, it has to be noted that a number of studies still showed cardiac cycle effects even if stimuli were not cued but instead presented pseudo-randomly (19, 38, 39). Our finding of shared attention-related areas between pain perception and baroreceptor firing are in agreement with this conclusion and with others’ view that largest part of the fMRI responses elicited by phasic nociceptive stimuli may reflect non-nociceptive-specific cognitive processes (57).

In line with the view that expectancy and attention, rather than physiological habituation, modulate the baroreceptor gating of pain responses, attention-related brain areas were significantly more activated when participants reported to less pain. In our behavioral analyses, stimuli rated as less painful occurred at systole. This suggests that areas like the superior parietal lobule, precentral and lingual gyrus may be implicated in the association between pain perception and baroreceptor functioning via attentional mechanisms. These brain regions are indeed activated by pain (58), and are implicated as neural substrates of parasympathetic nervous system control (59,60).

In interpreting our results, one needs to be aware that in other domains, baroreceptor afferent firing does not have an inhibitory effect on the processing of sensory stimuli. For example, in the domain of

fear subjective, behavioral, and neural responses are greater at systole and attenuated at diastole (61). Unfortunately, the cross-sectional design of our study does not allow drawing causal conclusions about the inverse associations that emerged between dispositional characteristics like pain catastrophizing (and particularly helplessness thoughts when experiencing pain) and BP. Is it simply that people with higher BP perceive stimuli as less painful, and therefore have a less dramatic attitude toward pain? Intriguingly, pain catastrophizing was correlated with BP, which in turn was associated with reduced pain perception. Future studies with a larger sample size should investigate pain catastrophizing as a potential moderator of the BP-pain relationship. Considering that pain catastrophizing correlates with pain intensity of pain across chronic pain disorders, this might help clarifying the reason why BP-hypoalgesia disappears in chronic pain.

A major limitation of this study is the small sample size, which increases the likelihood that the estimate of the magnitude of a significant effect is exaggerated (62). Second, due to time constraints, pain threshold was not assessed at both systole and diastole. Third, BP was not monitored throughout the fMRI protocol due to technical difficulties in having reliable BP data in the scanner environment.

This is the first study to combine MRI and peripheral physiology monitoring with the aim of examining the link between BP-related hypoalgesia and baroreceptor functioning, therefore results should be considered preliminary and need to be replicated. Present results support the existence of a significant association between elevated BP and reduced pain perception. Moreover, our findings endorse the view that, in addition to regulating BP, baroreflex mechanisms modulate activity in pain-related brainstem areas (17). Research that elucidates the causal mechanisms underlying this phenomenon and its role in the pathogenesis of hypertension is highly relevant for the prevention of cardiovascular morbidity, the most widespread and costly health problem of the modern era.

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FIGURE CAPTION

Figure 1. (A) Event-related responses to pain stimuli. Three-dimensional surface-rendered projections of the activations associated with painful vs non-painful stimulation. SPM display threshold: p uncorrected = 0.001, minimum cluster size = 100 voxels. See Table 2 for the statistics associated with the significant main effect of painful stimulation. (B) Overall effect of baroreceptor discharge. Horizontal section and signal plot for the region in the left superior parietal lobe (SPL) that activated when the spontaneous discharge of baroreceptor was maximal. The signal plot shows that activity in this region was increased at systole (bar 1 and 2) than diastole (bar 3 and 4), irrespective of pain stimulation. The level of activation for the four event types is mean-adjusted (i.e., the four values sum to zero) and is expressed in arbitrary units (a.u. \pm 90% confidence interval). SPM display threshold: p -unc = 0.001, minimum clusters-size = 100 voxels.

Figure 1

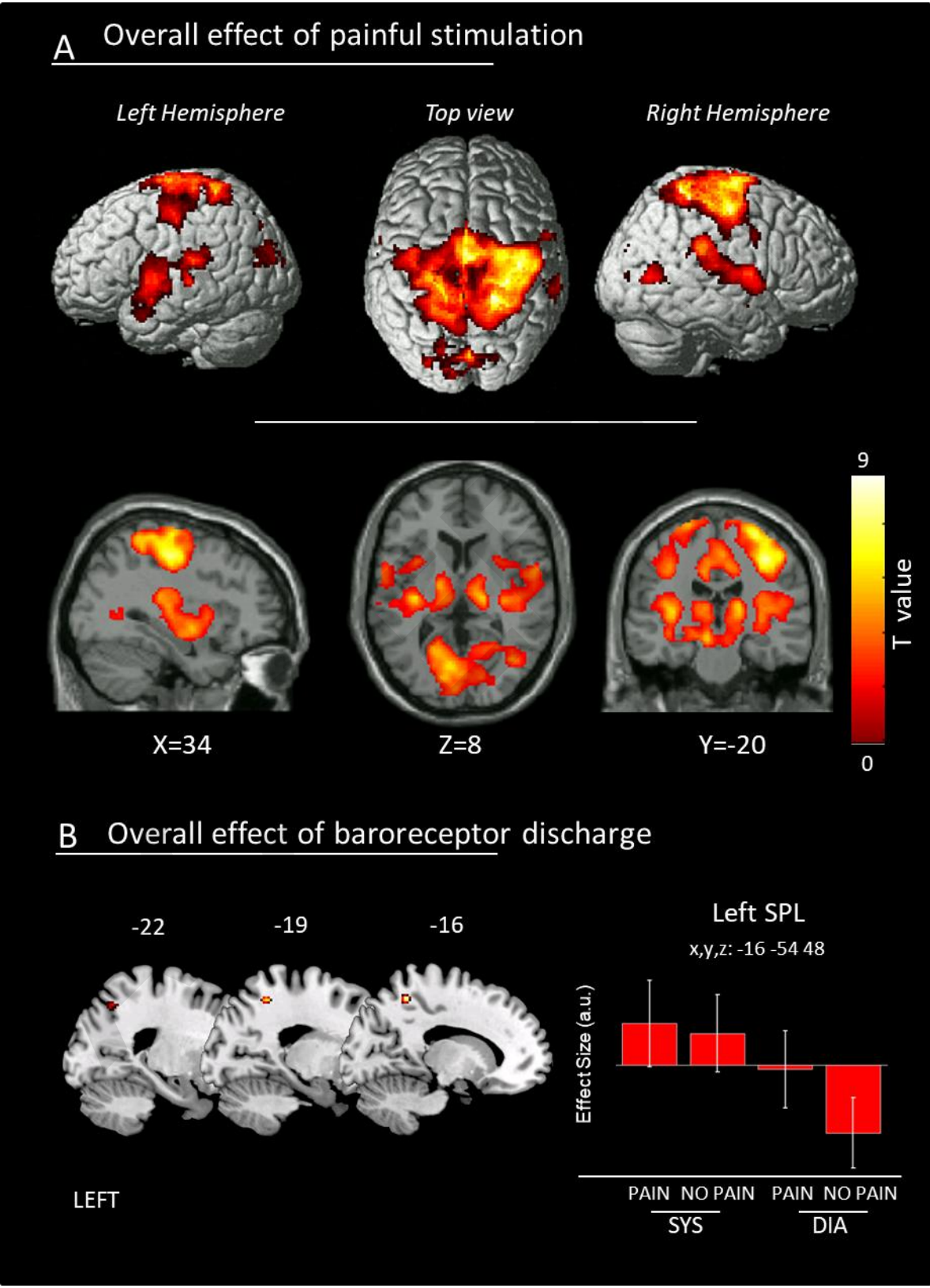


Table 1. Pearson correlations between dispositional characteristics and average weekly systolic blood pressure (SBP), pain threshold, and subjective pain evaluation (VAS). $N = 18$.

	STAI	CESD	PCS	PCSr	PCSm	PCSh	BPIs	BPIi	SBP	Threshold	VAS
STAI	1	.63**	.45*	.36	.41	.39	-.22	-.01	.07	.27	.07
CESD		1	.53*	.59*	.34	.39	.07	.09	.01	.13	.15
PCS			1	.88**	.75**	.87**	.10	.31	-.84*	.10	.47*
PCSr				1	.62**	.61**	-.02	.30	-.69§	.15	.51*
PCSm					1	.45§	.20	.36	-.65	.22	.50*
PCSh						1	.09	.19	-.91**	-.07	.25
BPIs							1	.44§	-.08	-.06	.20
BPIi								1	-.07	.10	.37
SBP									1	.79§	-.80*
Threshold										1	.19
VAS											1

Note. * $p < .05$; ** $p < .0001$; § $p < .07$. STAI = Spielberger Trait Anxiety Inventory; CESD = Center for Epidemiologic Studies Depression Scale; PCS = Pain Catastrophizing Scale; PCSr = Pain Catastrophizing Scale-Rumination; PCSm = Pain Catastrophizing Scale-Magnification; PCSh = Pain Catastrophizing Scale- Helplessness; BPIs = Brief Pain Inventory-Severity; BPIi = Brief Pain Inventory-Interference; SBP = Systolic Blood Pressure; VAS = Visual Analog Scale (during painful stimulation).

Table 2. Overall effect of painful stimulation. $N = 18$.

<i>Contrast</i>		<i>Pain > No Pain</i>		
<i>Anatomical Region</i>	<i>Hem</i>	<i>p-corr*</i>	<i>Coord</i>	<i>Z-val</i>
PreC	R	<0.001	40 -12 54	7.32
PostC	R	<0.001	36 -22 50	6.94
SPL	R	<0.001	16 -44 64	6.89
SMA	R	<0.001	4 -8 50	6.57
aMCC	R	<0.001	6 12 32	6.16
PreC	L	<0.001	-22 -24 76	5.90
SPL	L	<0.001	-22 -40 64	5.90
Precuneus	L	<0.001	-6 -44 62	5.90
pMCC	R	<0.001	8 -12 42	5.61
Cerebellum	R	<0.001	18 -54 -16	6.50
Cerebellum	L	<0.001	-14 -62 -14	5.91
Lingual Gyrus	L	<0.001	-8 -72 6	5.83
Lingual Gyrus	R	<0.001	10 -58 -2	5.74
Posterior Insula	L	<0.001	-34 -20 8	5.64
SMG	R	<0.001	52 -32 26	5.64
Thalamus	R	<0.001	16 -20 10	5.59
Hippocampus	R	<0.001	34 -4 -8	5.44
Thalamus	L	<0.001	-14 -12 6	5.24
Posterior Insula	R	<0.001	36 -28 20	5.10
Amygdala	R	<0.001	22 -2 -14	4.82

Hippocampus	L	<0.001	-22 -24 -8	4.72
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Note. Pain > Non-Pain: brain regions activated by pain stimuli, as compared to non-pain stimuli

*= *p*-values FWE-corrected < 0.05 (voxel level, whole brain). Coordinates are in Montreal

Neurological Institute Space. PreC: precentral gyrus; PostC: postcentral gyrus; SPL: superior

parietal lobule; SMA: supplementary motor area; aMCC: anterior midcingulate cortex; pMCC:

posterior midcingulate cortex; SMG: supramarginal gyrus.

Table 3. Overall effect of painful stimulation within each region of interest (ROI). $N = 18$.

<i>Contrast</i>		<i>Pain > No Pain</i>		
<i>Anatomical Region</i>	<i>Hem</i>	<i>p-corr*</i>	<i>Coord</i>	<i>Z-val</i>
S1	R	<0.001	40 -20 48	6.61
S2	R	<0.001	28 -40 62	6.33
Premotor Cortex (BA6)	R	<0.001	40 -12 54	7.32
Premotor Cortex (BA6)	L	<0.001	-22 -22 74	5.78
Parietal Operculum	R	<0.001	44 -30 18	5.36
Parietal Operculum	L	<0.001	-42 -32 16	5.14
Cerebellum	R	<0.001	18 -54 -16	6.50
Cerebellum	L	<0.001	-16 -50 -18	6.34
Insula	L	<0.001	-34 -20 8	5.64
Insula	R	<0.001	34 -22 10	5.03
Thalamus	R	<0.001	16 -20 10	5.59
Thalamus	L	<0.001	-14 -12 6	5.24
Middle Cingulate Cortex	R	0.014	6 12 30	5.01
Middle Cingulate Cortex	L	0.016	-4 16 26	4.42
Amygdala	R	0.010	22 -2 -16	4.72

Note. Pain > Non-Pain: brain regions activated by pain stimuli, as compared to non-pain stimuli within nine ROIs.

*= p -values are Bonferroni corrected for the number of the ROIs, and significance threshold set at $p < 0.05$. Statistics significant following Bonferroni adjustment for multiple comparisons are highlighted in bold. Coordinates are in Montreal Neurological Institute Space.